Introduction to Neuromodulation

– Welcome to another episode of the Reverse Inflammaging, Summit Body and Mind, Longevity Medicine. And I'm your host, Dr. Robert Lufkin. We've heard a lot about the nervous system and how we modulate it with lifestyle and supplements and other approaches. Today, we are going to talk to an expert in neuromodulation, but actually how you can directly manipulate and modulate the nervous system with technology. I'm so delighted to have JP Errico today with us who is the co founder of a company that makes devices specifically for vagal neuromodulation and is an expert in this area and many affiliated areas JP.

Welcome to the program. – Thank you for having me. I appreciate the opportunity. – It's so great to have you here before we get into the details. Maybe you could sort of set the stage and tell, ever tell our audience how you came to be interested in this fascinating area. – So it's a very eclectic background.

I appreciate the opportunity to explain it. I'm an engineer by training, I went to MIT and studied aeronautical engineering. I went off to Duke University and studied law and also studied mechanical engineering and material science, I ended up becoming a patent attorney very briefly.

JP Errico's Path into Vagus Nerve Research

And I was invited by my uncle who is a world renowned spine surgeon to work with him to develop a new set of products for spinal surgery. And we ultimately were a very inventive team and licensed products off.

They've done about 20 billion in sales. Along the way, I had the opportunity to work with a very well respected neurosurgeon who did deep brain stimulation for treating Parkinson's disease and essential tremor back in the late 90s.

And I was fascinated by the effectiveness of the therapy and the safety of it. And I knew that if I had the opportunity, I wanted to move into the field of neuromodulation and do something creative and innovative in it.

Um About four or five years after that first opportunity to learn about it, I was given the opportunity to start a new company and I knew that it was going to be in the neuromodulation space, but I didn't know what area we were going to focus on.

And I had the opportunity to read an article that was uh basically an article, an animal study in which they had taken dogs and they had sensitized the dogs to an allergen.

And they, when they did that, they created the opportunity to cause an anaphylactic reaction. And when they did that, they then um cut the vagus nerve in the animals and the animals survived and one of the things that, that neurosurgeon had told me was any time anybody has ever cut a nerve. And as a result of cutting the Nerve gained a clinical benefit, there's an opportunity to potentially stimulate the nerve instead and to gain the same benefit. And so in 2005, a group of us went to Columbia University and reproduce those results using a vagus nerve stimulator instead of cutting the nerve and were able to save the life of an animal that would have otherwise died of an anaphylactic reaction. And that is what star started me on the journey of understanding and, and working on the parallel paths of the autonomic nervous system as well as the innate immune system because it's, of course, the innate immune system that's involved in those sorts of allergic reactions.

– Yeah. It's such an interesting area and I know you've spoken about this before and maybe you could take a moment and just elaborate a little bit for our audience about, about your views on the, the innate immune system versus the adaptive immune system and maybe the proactive immune system also that you've spoken about.

– Yes. I think most people, especially in the post COVID era are aware of the various different aspects of the

immune system. We have the innate immune system, which is the very basic first immune system to have evolved.

It is uh sort of has the first job of going after pathogens and bacteria and viruses and, and injuries to heal. We have the adaptive immune system which when we hear about antibodies or T cell memory T cells or other things, they're the, they're the cells and the arm of the immune system that are involved in remembering what's happened to the body and being prepared for the next time that, that challenge comes to pass.

Innate Immunity, Microglia, and Macrophages

There's also the central nervous system and the central nervous system really evolved in part to protect us from injuring ourselves or being in situations where danger lurked. And so I refer to the brain as the proactive immune system where the nervous system is the proactive immune system because it allows us to prevent ever coming in contact with danger or injuring ourselves and other things.

So there's really three arms to the immune system and, and the justification I have for using that, that type of language or description is the fact that about 15% of the brain itself is immune cells.

There's tissue resident innate immune cells called micro glial cells and the role that they play in development and in maintaining uh tissues all throughout the body, but also in the brain. And the effect that they have on ultimately degeneration is so critical that to assume that the brain was anything other than an immune organ is uh is challenging, at least to me, from the perspective I have.

– And how did these micro glial cells relate to macrophages and other types of immune cells elsewhere in the body.
– So, macrophages are a wonderful cell type.

In fact, I think they're probably the most important cells in the body and it starts all the way back just a few days after conception when the very first cells to move into the nascent embryo, and at that point, the embryo is maybe three layers of cells.

There's a wave of cells that actually come from outside the embryo into it. And they're mad macrophages and macrophage progenitors and they build our organs, they literally build the vasculature, they build the brain, they build the liver, they build the heart, they build the skin, they build our bones and the role that they play in building those organs is maintained after we're born. And during childhood, helping us to grow into adults. And then as adults helping to maintain us and ultimately their failure through challenges and inflammation and other things that derail their normal function lead us to degenerative conditions, everything from frankly osteoporosis to Alzheimer's disease. And ultimately, it's their failure that leads to us dying. So, understanding how to control them and keep them doing the home a static tasks, the housekeeping things that keep us healthy um As best as possible is the goal of longevity, science and medicine.

– Yeah, it's interesting. A couple of our other speakers have discussed nitric oxide and the role that it plays interestingly not only with the blood vessels and the endothelial of the blood vessel lining, but also interestingly with the macrophages and also neuro degeneration. And it sounds like that may be related to the micro glial cells and the roles that the macrophages and immune system plays. That nitric oxide may be somehow involved in that as well. – Absolutely. And nitric oxide is one of a series of different molecules that have, have an effect on the immune system and on, on the nervous system. And can in short order can actually cause pain, can trigger migraines, it can be involved in in cardiovascular problems, blood vessel constriction, as well as in the longer run, promoting inflammation and being involved in the inflammatory process.

Inflammation, Stress, and Chronic Disease

So, controlling these molecules and using them sometimes you need them, sometimes you don't, but having the the immune system and the nervous system functioning together to make certain that everything is moving along in synchrony and in harmony is what we need to do. And that's where the nervous system really comes into play. – And so both the nervous system and the immune system are, are about inflammation and all.

So what, what exactly, let's just step back. What exactly is inflammation, what's going on there? What's its purpose? How does it work – And how it relates to the nervous system?

Sure. So, inflammation is a response that cells have both non immune cells as well as normal cells to either damage or to pathogens. In fact, there are receptors on the surface of all cells that are called damps damage associated molecular pattern receptors. So, if they sense damage or molecules that are associated with injury, they'll become activated, they're also pants which are pathogen associated molecular patterns. And there are receptors that are associated with those. So, bacterial infections, havasu certain character to them that these receptors will respond to and when those receptors are activated and they're very ancient, long preserved in evolution.

When these receptors become activated, it causes inside the cell, a cascade of different molecular interactions to lead to to the expression of cytokines which are chemicals that the immune system uses to, to communicate things like TNF alpha, I'll one beta aisle six, which are interleukin six and interleukin one beta.

These, these molecules uh cause the cell to change its behavior in and change its energy usage. So will also get a chance. I hope to talk a little bit about the effect of inflammation on mitochondria.

And also mitochondria is effect on inflammation. And inflammation itself has really wide ranging positive and negative benefits in the case of short term injuries.

It's critical for us to stem blood flow or to attack viruses or, or infected cells. That's all part of how the immune system functions, especially the innate immune system.

But when that inflammation lasts for a long period of time, I think of it as like a farmer, you know, a farmer might be called up to go serve in the army. Well, if he's only gone for two weeks on reserve duty, he can come back and the farm is still functioning normally and he can go back into normally functioning and, and serving the community with the farm.

However, if he's called away to war and he's gone for years, that farm will fall into disarray because the farmer isn't there to coordinate the activities, animals will roam away the, the the farm itself won't grow good food.

And when the farmer comes back from that war, he may be suffering with PTSD, he may be suffering with other problems. The same thing happens in the immune system, short stints of inflammation are healthy, longer stints of chronic inflammation lead to a disruption, not only of the tissue that's supposed to be supported by themselves, but also those cells themselves become disrupted.

They become either primed or otherwise injured. And we see this in, for example, concussions or traumatic chronic traumatic encephalopathy. The the injury you see associated with football injuries or people coming back from war where they've been injured in traumatic brain injury settings.

– Yeah, we, we've heard that from our other speakers to about, about stress and that stress, acute stress is good, healthy for the body and chronic stress is bad. It sounds like you're saying the same thing that inflammation can be good if it's acute and a healthy response to an insult, acute, meaning short term versus chronic, which means long term spread out over a long period can be harmful. How, how are, how is stress and inflammation related? – Excellent question.

And in fact, I think of them as really two sides of the same coin. When I talk to people about the effects of inflammation, I often talk about the fact that um stress as well as sleep deprivation can lead to exactly the same cellular response. So you can see an increase in those cytokines that we talked about. Things like tumor necrosis factor alpha.

Mitochondria and the Anti-Inflammatory Pathway

You can see those levels go up in stressful circumstances and you can see them go up in sleep deprivation

circumstances, the same way you would see them go up if you had a viral infection or a bacterial infection. So, there really is two sides of the same coin. And, and we don't think of them that way when we think about, well, you can manage stress and that's not going to make you sick.

But how many of us have experienced becoming ill as a result of stress? Well, it's because it's triggering the same response in your body. And I bring that back to that whole proactive immune system associated with the central nervous system and, and, and our cognitive processing actually becomes disrupted from both stress as well as inflammation, you can see cognitive dysfunction.

I mean, brain fog is something that people talk about associated with conditions like fibromyalgia and long COVID where their cognitive processes aren't functioning very well. And it's a function of the fact that inflammation has been chronic for a long enough period of time that it's actually disrupting the brain's ability to form long term memories. And for those micro glial cells to do what they need to do to build the network of new neural pathways to learn.

– So what you're saying is that the brain actually actually thinking or psychological effects can have direct effects on stress and the immune system and manifest with chronic diseases just from psychological effects through these types of mechanisms. Is that right? – Sure.

I mean, we all are aware of how psychological abuse, emotional abuse can lead to depression and can lead to measurable changes in neurotransmitter expression.

In the brain, for example, depression is often associated with serotonin. Serotonin is a neurotransmitter that's produced in the brain, it's also produced in the gut. But the brain has its own areas that produce serotonin and inflammation can actually disrupt serotonin synthesis as well as serotonin re uptake. So one class of drugs that's oftentimes given to people with, with depression are called S S R I S.

They're selective serotonin re uptake inhibitors. So their job is to block serotonin being pulled out of the synapse because you want to preserve as much serotonin as you can in those circumstances.

But inflammation is exactly the opposite. I joked that TNF alpha, which is that pro inflammatory cytokine is the equivalent of a selective serotonin re uptake enhancer. It actually builds more of the certain receptors that pull serotonin out of the synapse and it disrupts serotonin production and that has a downstream effect on melatonin because melatonin is a product of serotonin.

Serotonin is a product of tryptophan, which is an amino acid. And melatonin is a critically important chemical found throughout nature because of its role, not only in sleep but also in how mitochondria function.

So if you disrupt serotonin synthesis through inflammation and stress, you will also disrupt the energy balance within cells and disrupt mitochondrial function.

And in a short term, that's okay. But in the longer term, chronically, that leads to mitochondrial dysfunction, it leads to a lot of other degenerative conditions that are associated with that.

– Yeah, let's dive into that. That's fascinating. Maybe you could uh elaborate on just the basics of what mitochondria are and their role and then also the relationship between mitochondria and inflammation, as you said, and maybe mitochondria and stress as well.

– Sure. So mitochondria are fascinating little creatures and I actually call them little creatures because evolutionarily it's very low, likely that they were actually an independent life form.

They have the ability to take the waste product if you will of Glycol Asus, which is the first step in creating energy for the cell. Let me step back for a second. The primary energy unit or the currency of energy in cells is ATP and ATP is formed in the cells as a result of breaking down glucose. Typically, it's glucose that's being broken down. And like Alexis is carried out by pretty much all cells in the body. But it's a very inefficient process.

It leaves a lot of really highly energetic waste products. Mitochondria have the ability to take those waste products and produce oodles of energy. So as you can imagine, early on in evolution, there were a group of cells that could only do like Alexis. And then there were this other group of cells that had the ability to create lots and lots and lots of energy.

And they were eaten if you will by the cells that didn't do it very well. And they created this symbiotic relationship and it is evolved over, you know, more than a billion years for, for now, all of our cells have mitochondria in them.

And mitochondria are the energy power plants. If you will, in the cells, inflammation has the ability to disrupt the ability of those mitochondria to function properly.

How Vagus Nerve Stimulation Works

And so one of the downstream consequences of inflammation is mitochondrial dysfunction, but it's a bidirectional relationship when, when inflammation occurs. Yes, there's disruption to mitochondria.

But when mitochondria begin to become dysfunctional, they will trigger inflammation and actually, they can actually trigger program cell death. So when the mitochondria failed, there's two ways that they fail.

One way is that they will eject their DNA. So mitochondria have their own DNA. It's one of the reasons why we are pretty sure that they were their own life form.

They can eject that DNA into the cell and the cell sees that and views that as potential damage and will up regulate the inflammatory processes. So that's one way that inflammation can be triggered simply by mitochondrial dysfunction.

The other way that they become dysfunctional is the the electron transport proteins. And there's no quiz on this, but the proteins that are involved in electron transport can leak out of them and they leak out of them when the, when the balance of ions aren't correct.

And this is one of the ways and this is tying it back to the autonomic nervous system is one of the ways that we can regulate that is by enhancing parasympathetic tone.

So there's a special receptor called the alpha seven nicotine acetylcholine receptor. Again, no quiz on that, but there's their present on the surfaces of cells like Nate immune cells and they're also present on the surface of mitochondria.

And so when they're activated and they're activated by the release of acetylcholine, which is the neurotransmitter of the vagus nerve and the parasympathetic side of the immune system of the autonomic nervous system. When that acetylcholine is released, it binds to that receptor and it has through each of the various different locations that it's present. It has this anti inflammatory cell preserving effect. So, one of the ways that we, we know that we can kick start those cells to behave normally again, if they've been inflamed is to have that release of norepinephrine of, of acetylcholine and activating these receptors.

You know, even in our own language, we see this, you know, we tell people, you know, if they're stressed out, we say take a deep breath. We all know that doing meditation or yoga or yoga breathing techniques is a very positive thing for our health and for our stress levels.

And it's also true that those things are good for lowering our inflow inflammation levels. And that's all a function of activating that the stretch receptors that activate the parasympathetic side of the nervous system.

So it all ties together. It's a fascinating story. – Yeah. Now a lot of your work has been with the vagus nerve. So tell us what, what is the vagus nerve and how does it tie in with inflammation and stress and all these things that you've been talking about? – Sure, the vagus nerve is the 10th cranial nerves. So your brain stem has a series of nerve nerves that reach out to various different places, mostly in your head and neck.

But the longest nerve is the 10th cranial nerve. It's called the vagus nerve because of this Latin root, which means the wanderer because it's the longest of the cranial nerves, it wanders throughout your chest and abdomen, innovating various different organs and tissues.

What most people don't realize who are aware of the vagus nerve is that about 80% of the fibers that are in the vagus nerve and there are hundreds of thousands of them, about 80% of them are actually bringing information back up into the brain stem.

It's not a nerve where, well, there are aspects of it that bring information from the brain back down to the body. But it is the brain's primary source of information about how the autonomic functions are your heart rate, your your breathing, your kidney function, frankly, even your immune system and your metabolism are related. And all the information is being relayed back up into the brain stem through the vagus nerve.

Now, the brain functions in a way I refer to it as frequency coded. So it's not so much the strength of the signal that's important. Although that is, it's really more important about how, how rapidly or what frequency those nerves are firing.

And so it's possible to activate the vagus nerve through deep breathing by activating stretch receptors that will change the frequency with which the nerve is firing.

You can also do it manually or mechanically. You can gargle cold water for 20 minutes. Seems like a long throw to get, to get to doing that. Humming dancing, chanting, all of those things will activate it through the proximity of the nerve in your neck to your voice box and other things. You can also stimulate it manually.

There's an old technique in medicine which was called the deep carotid massage. And people would involve digging the thumb into the neck and rubbing the carotid artery.

It was actually a physician from upstate New York by the name of I think it's John Leonard, Orr James Leonard Corning. He might have been a member of the corning glass family, but he recognized that the nerve, the vagus nerve ran in that same sheath as the carotid artery. And that really had nothing to do with rubbing the, you know, the vasculature or the blood vessel.

It had to do with the fact that the thumb was activating the vagus nerve. And it was used to treat things like super ventricular tachycardia, which is a cardiac condition where your, your heart's beating very fast and it hurts.

And then also status epileptic asse, which is when you have a seizure that doesn't break. So people used to use this technique to, to fix that. And he said, you know, I think maybe it's really the nerve, not the blood vessel that we're activating. And so he was the very first person to come up with the idea of using electricity to stimulate the nerve.

Now, for my benefit and for the benefit of everybody today, he wasn't such a very good electrical engineer, brilliant scientists and, and and position, but he didn't have the the electrical engineering capacity to make uh device that would stimulate the vagus nerve correctly.

That took about 100 years for the first vagus nerve stimulators to be approved. And their implantable devices that are used to treat epilepsy, but they've subsequently become approved for a number of other conditions including depression and a non invasive device that I was involved in developing is actually used to treat migraine headaches and other headache conditions.

Clinical Uses and Device Application

Although we did study it a number of other things and of course, it has stress relieving and stress management benefits the same way deep breathing techniques do or meditation does.

– So the stimulating the vagus nerve then electrically somewhere along its course, will simulate the effect of deep

breathing and get the stress response and also immune response as well with it. – Yes.

So when you stimulate the vagus nerve aleck, there's a pathway that goes again, back up into the brain stem. It goes into an area called the nucleus tractors solitary asse again, nobody has to remember that.

But that's where a number of really important nuclei exist in the brain, one of which is called the locust cyril ius. The locus Aurelius is tiny compared to the 86 billion neurons in the brain. It's only a couple 100,000, but it has the most widely distributed network of neurons or projections into the brain.

It's the primary source of norepinephrine in the brain, which is a very important neurotransmitter. Another area that's also activated by the vagus nerve stimulation is called the nucleus bacillus of Maynard's.

And that much like the locus Aurelius is the primary source of acetylcholine in the brain. And so, when the acetylcholine is released, it has the effect of calming down the micro glial cells. Because again, acetylcholine is the neurotransmitter that's binding to those receptors that we talked about before the alpha seven nicotine acetylcholine receptors. And it down regulates inflammation, it corrects any dysfunction that's going on in the, in the mitochondria.

And it sets those micro glial cells which are innate immune cells on the correct path of doing their home. A static functioning. We've got research looking actually at animal models of Alzheimer's.

And you can see that in the Alzheimer's animals, when they become symptomatic, their micro glial cells in the brain are exhibiting all of this, of the characteristics of an inflamed immune cell.

And within just a matter of minutes after stimulation is delivered, you can see changes, morphological changes, shape changes and in and behavioral changes in those cells moving them back into the more normal function that you would expect of a healthy animal. – So, no, I didn't mean to interrupt.

Go ahead. – No, I mean, so the same thing that's happening in the central nervous system is also happening in the rest of the body. There's a reflex arc that was discovered by a brilliant scientist by the name and he's a physician, a neurosurgeon as well by the name of Kevin Tracy.

And Kevin Tracy is the discoverer of, of some of what I've talked about today. But he recognized this reflex arc that exists that doesn't just affect the central nervous system. It also affects the body.

And it down regulates pathological inflammation, whether it be autoimmune diseases. He's looking at rheumatoid arthritis and Crohn's disease as well as other people have looked at effects on heart disease, atherosclerosis, and other problems like fibromyalgia pain. We've looked at hypertension, we've looked at a number of other things in the periphery.

But most of the work that we've done is really centered on the central nervous system and things that are affecting both early life as well as late stages of life.

Things ranging from autism and schizophrenia all the way through to Alzheimer's and Parkinson's disease. – Well, so the stimulation of the vagal nerve then Takes those 80% of FF different fibers going back to the brain.

So it's a way of directly stimulating the brain from the periphery and then the brain stimulates the rest of the body. And so you get the effects throughout everything. There is that right?

– Yeah, it's bidirectional. But yes, there's a reflex arc that happens in the brain stem. That so the signal going up into the brain will then cause outflow from the dorsal motor nucleus of the vagus nerve down into the body to cause that anti inflammatory effect is called the colon ergic anti inflammatory pathway. – Oh and one of our other speakers spoke about the vagus nerve in, in the context of something called poly vagal theory or autonomic dis regulation. How does that tie into this?

Is this the same thing? – Very much so, in fact, I think you're referring to Stephen Porges, a brilliant vagal theorist if you will. And a lot of his work is um psychologically based.

And evolutionarily based. And I think a lot of the molecular work that really ties all of his theories together um is the work that I've been talking about in the central nervous system and peripherally. So you have that fight flight or freeze mode that he talks about. That is sympathetically driven.

That's the sympathetic arm of the, of the Vegas of the autonomic nervous system. And that's the opposite of the rest digest and restore side of the autonomic nervous system, which is the vagus nerve or the parasympathetic so yes, very familiar with his work and he's a brilliant, brilliant theorist.

– And so to use a device like this, you just apply it to yourself. I think you, you may have won there a sample one. We can look at that. It's a – Yes.

So this is the device. It's the Wellness version is referred to as True Vega. And it's available for purchase, what you'll do is you'll place a small the amount of electrode gel.

So it's gel that's provided with the device onto the electrode surfaces. And then you palpate for where you feel your pulse. Sort of technically, it's between your trachea and your sternal colloidal mastoi muscle, but it's basically where you feel your pulse place a little gel on there, rub it in on the neck there. And then activating this, this button here will cause the, the device to turn on and then everybody's anatomy is a little different. You turn up the amplitude of the signal to the point where first you'll feel a tingling at the skin and then it will sort of move away from the skin and move into the muscle and you'll feel a little vibration of the muscle.

And once you get to a strong enough amplitude, most people will feel the corner of the mouth pulled down that's associated with the platinum A muscle, which is sitting right in the neck there and controls the corner of your mouth, it happens to sit in close proximity to the vagus nerve.

Benefits, Safety, and Biomarkers

And so we know that when your corner of your lip pulls down like this, you know, while you're doing it, that that indicates that you've activated the vagus nerve.

And the moment you pull the device away, that effect goes away. But the longer term effects of what you've done to the central nervous system and to this, this vaguely mediated pathway can last for hours.

And in fact in some studies, even days, we did a study talking about looking at cardiac vagal tone, which is around heart rate variability. And we were able to increase heart rate variability, increased cardiac vagal tone after a 12 minute stimulation that lasted out 24 hours.

So it is we generally suggest people use it twice a day. You know, sort of when you brush your teeth in the morning and the evening. And it will have sort of an effect that lasts over the full 24 hours of your day.

– And so what we're talking about here is a use for kind of the general public for wellness and longevity and not necessarily a pathological condition.

I mean, other than inflammation, which we, which we all have, which is a pathology that we all get with aging, but that somebody that, that regular people could apply. What, what are the contraindications for, for this. So there are certain people who shouldn't use it or is it pretty much available for anyone?

– So it's pretty much available for everybody. We were targeting adults. Obviously, there's pediatric indications that the prescribed version of the device, which is again is called gamma core.

That is specifically provided uh prescribed for migraines and other severe headache conditions like cluster headache, for example, can be used both acutely and preventatively. But the the precautions include things like if

you've had a previous surgery on your neck and there's metal in your neck, it's not guaranteed that it's going to cause a problem, but it's contra indicated because there's always the concern that there could be some heating effect of the electric coupling between the device and a metal implant in the neck hasn't been observed, but it's a theoretical risk.

And therefore we contraindicated for that contra indicate if the person has had a prior surgery that's cut the vagus nerve because in that situation, it's not going to be useful. You know, those are, those are the sorts of things that, that we would contraindicated.

But for most other people, it's a very benign and, and low risk treatment. – You know, what sort of, I mean, I guess inflammation is notoriously hard to measure with objective markers.

Is there any effect you see like on c reactive protein or any markers like that or what, what sort of results are you seeing with this. – So, yes, c reactive protein vagus nerve stimulators have been studied, including ours looking at markers like those cytokines that we've talked about TNF alpha I 01. And there's published literature around um all vagus nerve stimulators having that effect, whether they're implanted or non invasive like ours. But there's also effects that we've seen on metabolic uh measurements, things like HB A one CS on lowering of blood pressure. And, you know, there's, so there's a number of different markers that you can look at.

I'm interested for those gastroenterologists out there and people with IBD, we're, we're very interested to hear about the effects it might have on fecal cal protecting levels, which is a marker that's measured in people who have inflammatory bowel disease because there's data out there suggesting that it has that effect to, it will lower those levels, which is consistent with the lowering of stress and lowering of inflammation. So there's plenty of markers out there.

You can look at. Sure. – I mean, interested in the psychological effects on that. You mentioned it was used for depression for the implanted devices. What's, what are the difference in effects of the implanted ones, which is obviously a much bigger procedure versus the topical ones for psychological conditions like depression or other other things?

– Yeah. So all of the data that we've collected, whether it be in animal models, multi, studying the implanted devices versus the non invasive have all shown exactly the same effects both clinically and pre clinically. Measurements of activation of areas in the brain stem. We've done EEG studies, we've done FMRI studies. All of which seem to indicate that whether it's implanted or done topically, it has the same effect on the nerve.

Of course, not all of those are our large clinical studies. They're more pre clinical studies, but there's no reason that I know of as a scientist to believe that there's any difference between the implanted device in its activation of the vagus nerve versus a non invasive – And for a person to use it in this topical application. What sort of things do they experience after? I mean, obviously they, you mentioned the pulling on the plate is more muscle and all, but like after they begin to use it, do they feel effects of well being or any other?

Are there any other effects? Are there any other side effects also that we should be watching out for? – So, yes, there's def definitely a feeling a lot of patients will talk about a feeling of stress release in the neck area, they'll feel just looser. We've got chiropractors who use it to say that when they're dealing with a person who has a high level of stress, it's very difficult to do the manipulations that they do and within just a minute or two after stimulation, they feel as if the muscles have just turned to butter, they're much more relaxed. There's also effects that have been studied by the defense department and published around cognitive enhancement.

Psychological and Cognitive Effects

And I realized that for some people that may sound very star Trekkie, but there was a $100 million program that DARPA which is the defense advanced research projects agency ran looking at various different neuromodulation products, looking to see if any of them could actually enhance a person's intelligence.

And I'm happy to say that our device came through that work very positively. And it's been published demonstrating

anywhere from a 25-40% improvement in learning capacity. And the application of that learning and the rest of the formation of memories out and tested out 90 days.

So there appears to be and I understand you know why that would be the case. But there appears to be at the top level cognitive benefit, a cognitive enhancement benefit associated with vagus nerve stimulation.

The flip side of that is, well, what happens in inflammation and what does inflammation due to damage neuro development? And that's where we're doing some, some really interesting work right now, looking at the consequences of neuro inflammation or inflammation on neuro development. And that's where I talked earlier about autism and schizophrenia at the early stages of life.

And then at the end of life, sort of, of a reversion of those innate immune cells to sort of a second childhood if you will reverting back to doing some of the things that are really only appropriate during Euro development, but result in neurodegenerative conditions like Alzheimer's and Parkinson's disease.

That's why when you talk to some of the neuroscientists and neurologists who are working on Alzheimer's, one of the things they talk about is anything that works for.

Schizophrenia looks like it has benefits. And Alzheimer's, and the reason for that is because it's exactly the same mechanisms that are taking place really exciting stuff. – Yeah, it's fascinating.

We had Chris Palmer as one of the speakers, a psychiatrist from Harvard using ketogenic diets for schizophrenic patients. And those are the same ketogenic diets that are so effective in Alzheimer's, Dale Bredesen was a guest here also.

And it's amazing the overlap with inflammation and all these common threads that affect our longevity that are controlled by this. You mentioned it was effective for migraine headaches.

I assume other headaches too. As well. – Yes, severe headaches. It's been studied in severe headaches like cluster headache, which is referred to as the suicide headache.

It is a terrible condition that affects largely men. About two out of three or even three out of four sufferers are male. Um But it's the suicide rate among that patient population is 20 times higher than the national average. It's a brutal disorder.

If you've ever seen somebody suffering with one of those headaches, it's difficult to watch. So we that's actually the very first thing we went after to get a clinical approval because we felt that patient population was in desperate need.

– Yeah. Now, understanding that, I guess neck pain can have many, many causes and depending on the cause. But, is this something that's effective for any sorts of neck pain that comes along?

– Yeah, cervical genic headaches, you know, one of the reasons why women suffer with more migraines than men is because they tend to carry stress in their neck.

The neck muscles become very, very tense, sort of, sort of permanently locked, nodded. And that, that stress ends up through, you know, cervical nerve roots ends up leading to migraine headaches. And so one of the reasons that I personally believe we were successful in getting approval and showing in our, in our studies how effective it can be is because of that ability to relax the neck muscles. So, absolutely.

– And there's so much promise for this, so much effectiveness across inflammation, across stress, all these different things. What sort of resistance are you encountering? Why isn't this more widespread?

Why, you know, why isn't everyone using this everywhere? What is the pushback and what are you doing about it? – There hasn't been a tremendous amount of pushback from patients or clinicians.

In fact, most clinicians who have heard about it and learn about it are fascinated by it. And want to try it. The issue has been largely around reimbursement. You know, most people in the United States have insurance and expect to have insurance cover things and, and that's a dance that large companies have the opportunity to do very well in, in small companies sometimes have challenges.

I think that going into the space with a product that's priced at a space, a place where people can afford it themselves is going to give us an opportunity to, to expand the usage tremendously. And I'm looking forward that it's a, it's a really only within the last, you know, few months that we've been selling the product through that channel directly to patients. Of course, you know, the military has been one of our biggest, biggest buyers frankly, of the product. They, they recognize the value and they're, they're freely using it.

Future Research and Closing Remarks

– And in this direct consumer product, I assume that like that if you had a family that everyone in the family could use it, just observing sanitation stuff, you just wipe it off, wipe the electrodes off and reuse it.

Right. – Yes, I mean, our hope is that the same way people don't share toothbrushes, they won't be sharing their stories but, or their true Vegas. But, but you're certainly right there, there is that option and, and I've, I've seen it in my own house.

So, yeah. – Well, since you mentioned what is your personal routine if I can ask? Like, how do you use it and what benefits have you seen yourself from? – You know, I'm fortunate enough that I don't have a lot of the symptoms. However, when I it's usually during a period of significant life stress where, you know, like, like most men, my age, I get up in the middle of the night to go to the bathroom.

And when I get back to bed, if I've got a lot of stress and things on my mind, I have a difficult time falling back to sleep. And what I found is that if I use it, I will be back to sleep within a matter of minutes.

So I think it's that's my own personal testimonial. I can tell you that it's been very beneficial for stress management for my wife as well. And the cognitive enhancement benefits have certainly helped in the house. I've got some kids who have used it as well and I'm very pleased with how I've seen the effects on them because I really truly believe that ultimately, one of the key benefits of vagus nerve stimulation is going to be neurodevelopmental optimization. I think we have a very serious problem right now in the United States, I think it's a ticking time bomb.

We've all seen the reports about autism rates that are skyrocketing. I think that's a function of maternal immune activation and maternal inflammation and early childhood inflammation and there's plenty of data to demonstrate that.

But I also think that schizophrenia which usually doesn't exhibit itself until, you know, 15 to 25 years later. I think that's a ticking time bomb that is going to affect us in another decade or so. We're going to see schizophrenia rates rise dramatically. You heard it here for, I'm predicting it.

And given the fact that mental health is such an important thing for the for the country to be addressing whether it be homelessness or mass shootings.

Mental health is a really major problem and the data is out there demonstrating that if we can reduce um inflammation and infect During pregnancy, we can reduce schizophrenia rates by 30% or more.

And unfortunately, I think we're going in the opposite direction. I think that there's a lot more inflammation and a lot more um risk of pregnant women being under high stress or under, you know, under inflammatory conditions.

I think there's a big problem coming. – It sounds like this is an area ripe for prospective trials in this area. Are there any going on now or is this something yet to be yet to be done?

Using this type of technology to reverse or diminish maternal impairing natal inflammation. – Yes. In fact, I'm

partnering with really a world renowned scientist, basic scientists up in Canada, who she's got models of both schizophrenia and autism in animal models where they do exactly what we've been talking about, generate an inflammatory insult while the animal is pregnant. And what they see in the off offspring is not only the behavioral symptoms of autism or schizophrenia depending on when the insult is, is delivered, but it also has an effect. By physiologically, you can actually do the postmortem analysis of the central nervous system.

And you see the same structural anomalies that you see in autism and schizophrenia in humans. And so what we're doing is we're doing a study to look, to see whether or not vagus nerve stimulation delivered during that period has the ability to protect the offspring against that immune activation.

And there's reasons to believe that it will work because we've seen it in headache models where we've taken animals and sensitize the animals so that they become migraine yours.

And we can prevent that sensitization from occurring and from taking hold by using vagus nerve stimulation in those models. So I'm, I'm cautiously optimistic that the benefits will be there.

I'll come back next year and tell you. – Well, we've covered so much interesting material here in this hour. How can people if they want to learn more about your work, how can they follow you on social media or what is your, what is your website?

– So, for the device, it's easy. It's truvega.com. That's T R U V A G A.com. So that's what they want to get a device. But there's also the Vagus Nerve Society.

And I'm doing a podcast with my partner Dr. Navaz Habib. The podcast is called the Health Upgrade. And so we welcome everybody to listen in on that. And then of course, I'm in the process of writing a book.

Actually, it's a companion book with a book that my podcast co host is also writing. So the two of us will have two books that will come out together.

He's focusing on the clinical aspects and I'm focusing on the more scientific aspects and historical aspects of vagus nerve stimulation. So should be exciting. – Great. Well we look forward to having you back to talk more about that when that comes out. So, thanks so much JP for spending an hour with us and thank you so much also for all the, all the great work you're doing.

– It was a pleasure speaking with you. And as I said, I look forward to updating everybody in do course.